Applicants maintain for the reasons set forth in the following remarks that claims 1-8 of the subject application are presently in allowable form, and applicants respectfully request that the Examiner reconsider and the rejections of the claims and allow the present claims based on the following remarks.

REMARKS

In the June 20, 2000 Office Action, the Examiner rejected claim 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Arnold, et al., U.S. Patent 5,670,516. The Examiner asserted that Arnold et al. teaches a method of treating neurological disorders by administering a compound that blocks or antagonizes AMPA receptors. According to the Examiner, the invention recited in the claims of the present application is directed to a more specific neurological disorder, namely dyskinesia associated with dopamine agonist therapy. The Examiner stated that a person of ordinary skill in the art would have been motivated to treat dyskinesia [associated with dopamine agonist therapy] using an AMPA receptor antagonist in view of Arnold et al. because Arnold et al. supposedly teach that dyskinesia is among the neurological disorders responsive to AMPA antagonists (citing claims 24 and 29 of Arnold et al.).

Applicants respectfully traverse. Arnold et al. refers to a list of "neurological disorders", including "tardive dyskinesias" in Column 3 that can be treated by the compounds of formula I therein indicated to be AMPA receptor antagonists (see Column 3, lines 30-46). Although the Examiner pointed out that "mechanisms of action as to how a particular condition, disease, etc. works are not afforded patentable weight under the current U.S. law", this precept is not applicable to the instant facts. Here, applicants are urging that the *indication* referred to in Arnold is qualitatively different from the *indication* recited in applicants' claims. Arnold et al. refers to tardive dyskinesia, whereas the claims of the subject application relate to dyskinesia caused by dopamine agonist therapy. The aforementioned rule which the Examiner has set forth applies to facts wherein the indication is the same, albeit caused by two different mechanisms.

Tardive dyskinesias are qualitatively different from "dyskinesias associated with dopamine agonist therapy" which is recited in applicants' claims. In the

specification of the subject application, "dyskinesia associated with dopamine agonist therapy" is defined as any dyskinesia which accompanies, or follows in the course of, dopamine agonist therapy, or which is caused by, related to, or exacerbated by dopamine agonist therapy (see page 3). "Dyskinesia" in turn is defined in the specification as any abnormal or uncontrollable movement including, but not limited to, chorea, tremor, ballism, dystonia, athetosis, myoclonus and tic (see page 2). Thus "dyskinesia associated with dopamine agonist therapy" is any abnormal or uncontrollable movement which accompanies, or follows in the course of, dopamine agonist therapy, or which is caused by, related to, or exacerbated by dopamine agonist therapy.

Tardive dyskinesias, which are recited in Arnold et al., are not dyskinesias associated with dopamine agonist therapy. Tardive dyskinesias may be found in patients undergoing dopamine antagonist therapy, such as for example patients suffering from psychosis being treated with a dopamine antagonist. Attached hereto is a copy of pages 1197-1200 of R. D. Adams, et al., Principles of Neurology, Sixth Edition, (McGraw-Hill Companies. Inc., 1997). These pages of Adams et al. describe certain antipsychotic drugs and some side effects thereof. On page 1198, information regarding phenothiazine drugs, which are dopamine antagonists, is provided and it is stated that "the following types of extrapyramidal symptoms have been noted in association with all of the phenothiazine drugs [as well as with the butyrophenones and, to a lesser extent, the neuroleptics metoclopramide (Reglan) and pimozide, which have the ability to block dopaminergic receptors]". In this regard, page 1199 describes the particular side effect "tardive dyskinesia" as "lingual-facial-buccal-cervical dyskinesias, choreoathetotic and dystonic movements of the trunk and limbs, diffuse myoclonus (rare), or perioral tremor ("rabbit" syndrome), dysarthria or anarthria" which "may occur as late and persistent complications of neuroleptic therapy "and which "may continue after removal of the offending drug" (page 1199, first column).

Hence, it is apparent that tardive dyskinesia are a different indication than "dyskinesia associated with dopamine agonist therapy" which is recited in the claims of the subject application. Accordingly, applicants maintain that it would not be obvious from Arnold et al., which recites "tardive dyskinesia", that an AMPA

receptor antagonist would be useful for treating dyskinesia associated with dopamine agonist therapy.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Klockgether, et al. The Examiner stated that Klockgether et al. teaches that blocking AMPA receptors by administering AMPA receptor antagonists may provide a new strategy for treating Parkinson's disease. The Examiner argued that a person of ordinary skill in the art would have been motivated to develop a method for treating dyskinesia associated with L-dopa therapy based on Klockgether et al. because Klockgether et al. supposedly suggests treating Parkinson's disease patients who are on L-dopa therapy and that AMPA antagonists can potentiate the actions of l-dopa and reduce tremor associated therewith. The Examiner also argued that Klockgether et al. suggests treating dyskinesia associated with l-dopa therapy since Parkinson's disease symptoms include tremors which results in dyskinesia. The Examiner characterized Klockgether et al. as teaching that co-administration of an AMPA antagonist and L-dopa was conducted to reduce symptoms typically associated with Parkinson's disease, including tremors and dyskinesia; and that, in such co-administration, the AMPA receptor antagonist potentiates or makes l-dopa more effective in the treatment of Parkinson's disease symptoms because "it reduces or eliminates side effects associated with the administration of either antagonist or l-dopa drug", citing page 720, first column, lines 8-10.

Applicants respectfully traverse. First, Klockgether et al. does not state at page 720, first column, lines 8-10, that NBQX (the AMPA receptor antagonist) reduces and/or eliminates side effects associated with the administration of l-dopa. The reference merely states at the cited portion, "no NBQX-related side effects (dyskinesias, vomiting, or apparent psychological disturbance) were seen in either monkey". Thus, all that is stated is that the AMPA receptor antagonist, NBQX, did not present any side effects. Nothing here is mentioned or implicated about reducing or eliminating l-dopa side effects. Granted, one of the monkeys (referred to as monkey No. 920) to which the cited statement refers was a monkey with experimentally-induced Parkinson's disease which had been administered NBQX in combination with l-dopa. However, the l-dopa was administered at a dose that had alone produced only marginal improvement [in reducing parkinsonian symptoms] (see

page 719, second column, the last three lines, of Klockgether et al.). There is no mention in Klockgether et al. that this monkey ever exhibited side effects due to the l-dopa administration. In fact, there is no mention that this monkey exhibited any side effects.

Klockgether et al. does indicate that this monkey "had severe parkinsonian rigidity in the left upper extremity" caused by the experimentally-induced Parkinson's disease (not either NBQX or l-dopa) (page 719, second column, the last paragraph, which continues on page 720). Klockgether et al. indicates that subsequent to a low dose of NBQX combined with a dose of L-dopa that that had produced marginal improvement, the monkey was able to open it left hand for the first time since receiving the initial parkinsonian-inducing MPTP injection (pages 719-720). Rigidity is a clinical feature of Parkinson's disease. This is supported by pages 1067-1070 of Adams, et al., supra, attached hereto. Page 1068 of Adams et al. (the first column), referring to Parkinson's disease, states "the core syndrome of expressionless face, poverty and slowness of voluntary movement, "resting" tremor, stooped posture, axial instability, rigidity, and festinating gait has been fully described in Chap. 4, and only certain diagnostic problems and variants in the clinical picture are considered here". However, "rigidity" is not associated with dopamine agonist therapy, which is recited in the claims of the subject application. Attached hereto also are pages 1073 and 1074 of Adams et al, supra, which provides information relating to L-dopa therapy. On page 1073, it is stated that "the most common and troublesome effects of L-dopa, requiring individualization of therapy, are end-of-dose failure, the "on-off" phenomenon, and the induction of involuntary movements -- restlessness, head wagging, grimacing, lingual-labial dyskinesia, and choreoathetosis and dystonia of the limbs, neck, and trunk." Rigidity is not mentioned. Moreover, more generally, rigidity is not even a dyskinesia; rigidity is absence of movement, whereas dyskinesia refers to presence of movement, albeit abnormal.

Hence, it can be seen from the above discussions that the movement indications observed in dopamine agonist therapy are different and entirely distinguishable from the features observed in patients with Parkinson's disease. Thus, applicants maintain that the claimed invention is not obvious from Klockgether et al., and again reiterate that the claimed invention is also not obvious from Albert et al. At

most, Klockgether et al. suggests that an AMPA receptor antagonist, NBQX, can be combined with dopamine agonist therapy to treat the symptoms of Parkinson's disease. It does not suggest that an AMPA receptor antagonist could be used for treatment of the effects of dopamine agonist therapy, such as dyskinesias associated with dopamine agonist therapy.

Applicants furthermore maintain that Klockgether et al. suggests that use of an AMPA receptor antagonist might actually result in dyskinesia such as those observed in chronic dopamine replacement therapy, e.g. dystonias and choreic dyskinesias (see the "Background" section of the subject application). Klockgether et al. also suggests that use of an AMPA receptor antagonist might actually aggravate such dyskinesias brought about by l-dopa therapy. It is noted that Klockgether et al. states that "[t]he principal findings of this research are that the selective AMPA receptor antagonist NBQX has potent antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys and that it potentiates the actions of L-dopa". Since NBQX is thus implicated in Klockgether et al. to have effects such as those produced by L-dopa, e.g. reduction in severe rigidity that is symptomatic of Parkinson's disease, it would seem to follow that NBQX might be expected to have the same side effects, e.g. choreic dyskinisias and dystonias, brought about by L-dopa therapy. True, Klockgether et al. further states, "NBQX did not produce apparent side effects *at the doses tested*" (emphasis added). However, applicants do not see how this statement provides insight or implication as to what effect NBQX would have at other doses or when chronically administered. Applicants point out that the example (Example 1) in the specification of the subject application clearly demonstrates, however, that an AMPA receptor antagonist can reduce dyskinesias induced in a monkey by dopamine agonist administration (L-dopa and PHNO).

The Examiner noted that Klockgether et al. states on page 723 that "[s]elective AMPA receptor antagonists have recently been reported to prevent neurotoxicity of L-dopa in an in vitro test system, and that they may therefore prevent some long term adverse effects of L-dopa treatment". This statement mentions neither "treatment" nor "dyskinesia associated with L-dopa therapy". It therefore does not render obvious use of an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy, as claimed herein. Klockgether et al. provides no assertion

or suggestion that neurotoxicity is relevant to dyskinesias which are observed in patients treated with a dopamine agonist. There is no evidence that dyskinesias are related to neurotoxicity.

The Examiner also rejected claims 1-3 and 5-7 under 35 USC 103(a) as allegedly obvious over Stella, et al. in view of Klockgether, et al., supra. The Examiner stated that Stella, et al. teaches administering glutamate antagonists to treat dyskinesias associated with l-dopa therapy in Parkinson's disease. The Examiner further stated that claims 1-3 and 5-7 differ because they recite administration of an AMPA receptor antagonist "as the glutamate antagonist". According to the Examiner, it would have been obvious to one of ordinary skill in the art to use AMPA antagonists as a glutamate antagonist, rather than "the NMDA antagonist". The Examiner asserted that one would have been motivated to make the substitution because Klockgether, et al. teach that both AMPA antagonists and NMDA antagonists are glutamate receptor antagonists, citing page 1, column 2, of Klockgether, et al. The Examiner further alleged that applicants argued the Stella et al. and Klockgether et al. references separately and attacked the references individually.

Applicants respectfully traverse. Column 2 on page 1 of Klockgether et al. does not state that an AMPA receptor antagonist is a glutamate antagonist. Regardless, the discussion in Stella et al. regarding dyskinesia produced by levodopa/benserazide therapy is restricted to NMDA receptor blockade. Applicants noted in their last response that the statements in Klockgether et al. do not compensate for this deficiency, i.e. the limitation to NMDA receptor blockade, in Stella et al. because Klockgether et al. does not suggest that an NMDA receptor antagonist can be replaced with an AMPA receptor antagonist with the expectation of producing the same effect. This is not arguing the references separately. In that regard, column 2 of page 1 of Klockgether et al., if anything, suggests differences between AMPA antagonism and NMDA antagonism. More particularly, Klockgether et al. states at column 2 of page 1 that l-glutamate antagonists acting at the NMDA receptor have thus far been ineffective as anti-parkinson agents when administered systemically to primates. Klockgether at al. further states that since AMPA receptors are enriched in the subthalamic nucleus in comparison to NMDA receptors, AMPA antagonists may be effective in reducing activity of neurons in the STN. Accordingly, applicants

maintain that it is not obvious from Stella et al. in view of Klockgether et al. to treat dyskinesia associated with dopamine agonist therapy using an AMPA receptor antagonist.

In conclusion, applicants maintain that claims 1-9 are directed to an unobvious inventions and that claims 1-9 are in condition for allowance. Applicants respectfully request the earliest possible notification of allowable subject matter.

If a telephone interview would assist in the prosecution of the subject application, the Examiner is invited to telephone applicants' undersigned attorney at the telephone number provided.

No fee is believed necessary in connection with filing this Communication. However, if any fee is determined necessary in connection with filing this Communication, authorization is hereby given to charge such fee to Deposit Account No.16-1445.

Respectfully submitted,

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